Eur J Cancer Clin Oncol, Vol. 17, No. 9, pp. 969–990, 1981.
Printed in Great Britain.

0277-5379/81/090969-22$02.00/0
Pergamon Press Ltd.

Perspectives in Cancer Research

Paraneoplastic Syndromes*

H. J. TAGNON and J. HILDEBRAND
Institut Jules Bordet, 1000 Bruxelles, Belgium

Abstract—*There are two types of clinical and biochemical syndromes not directly associated with the invasiveness and metastatic ability of the tumour; the first type is represented by the hormonal paraneoplastic syndromes. The second type consists of certain neurological diseases or abnormalities observed in patients with malignant tumours not directly affecting the nervous system. While the hormonal type is well established and rests on solid ground, the neurological type is less well defined and more controversial.*

I. Endocrine Paraneoplasia

H. J. TAGNON

1. INTRODUCTION

THE TITLE delineates the content of this article, which is a discussion of the ectopic production of hormones by neoplasms. These hormones may create clinical manifestations which are apparent to the physician; or they do not give rise to a clinical syndrome but are detected by direct measurement in blood or in the tumour itself. Ectopic production means the secretion of hormonal products by tumours arising from tissues not normally producing them. For instance, secretion of insulin by a pancreatic carcinoma is not an ectopic production and does not create a paraneoplastic syndrome in the strict sense of the word: it is a 'eutopic' production. The eutopic secretion of a tumour may be difficult to distinguish from an ectopic production, or in some instances the same tumour arising in an endocrine organ may secrete at the same time the natural product of this endocrine organ and one or several other hormones which are not normally produced by this particular organ and therefore deserve the ectopic qualification. Ectopic hormones are polypeptides or proteins. Finally, certain types of neoplasms produce non-hormonal compounds not found in normal adult tissues which have antigenic properties and are used as 'markers'. They are detected in the body fluids by immunological methods and are at the present stage of development of limited assistance to the clinician for the diagnosis and monitoring of the evolution of the tumour.

These non-hormonal markers are not the subject of this review. However, ectopic hormones are also 'markers' and are increasingly utilized in clinical medicine for diagnostic and prognostic evaluation of patients.

There are several excellent reviews on this subject. The reader is referred to them for details on the biochemical aspects of endocrine paraneoplasia [1–5]. These reviews present diverse interpretations of the mechanism at the cellular level of the phenomenon of ectopic hormone secretion and these will be summarized here. However, our aim is essentially to present the aspects of paraneoplasia which are of interest to the clinicians and will help them understand the problems presented by their patients. It is obvious that the biochemical aspects and the research methodology are also

*Supported in part by National Cancer Institute (Bethesda, MD) contract no N01-CM-53480.

Abbreviations: ACTH, adrenocorticotrophin hormone; ADH, antidiuretic hormone; APUD, amine precursor uptake and decarboxylation; AVP, arginine vasopressin; CLIP, corticotrophin-like intermediate lobe peptide; 5 HT, serotonin; FSH, follicle-stimulating hormone; GH, growth hormone; hCG, human chorionic gonadotrophin; HPL, human placental lactogen; RNA, ribonucleic acid; LPH, lipotrophic hormone; MSH, melanocyte-stimulating hormone; NSILA, non-suppressible insulin-like activity (somatomedin); PTH, parathyroid hormone; MSA, multiplication stimulating activity; CRH, corticotrophin-releasing hormone; OSF, osteoclast-stimulating factor; CEA, carcinoembryonic antigen; αFP, alpha foetoprotein; TSH, thyroid stimulating hormone and 5 HIAA, 5-hydroxyindoleacetic acid.

of great interest to the clinician insofar as he accepts to being a biologist willing to try to understand cell biology and general endocrinology in order to be able to apply this knowledge intelligently and to follow the progress of research as it is published in medical journals. Therefore, our presentation should be considered as an introduction to the subject and the bibliography as an incitement to broader reading.

2. DEFINITION OF ECTOPIC PRODUCTION OF HORMONES

There are now available sensitive immunologic techniques permitting large scale screening of sera for specific hormones from patients with documented tumours of non-endocrine origin. Every known glycoprotein or polypeptide hormone has been identified in these syndromes. Therefore it is most important methodologically to set up criteria to distinguish between hormones produced by the normal endocrine organ and abnormal secretion by tumours from tissue having no endocrine function.

A hormone found in the body fluids can be said to result from an ectopic secretion if the following criteria are satisfied:

(i) there is greater concentration of hormone in the tumour than in surrounding normal tissue;

(ii) the hormone can be localized in the tumour by immunological or biochemical methods;

(iii) the hormone disappears after removal of the tumour and reappears if the regrowth of the tumour occurs;

(iv) there is an arterioso–venous difference in hormone concentration across the tumour bed;

(v) it may be possible to detect and measure the production of the hormone by the tumour *in vitro*.

These criteria are useful in most situations. However, they should not be considered as absolute in view of our present fragmentary knowledge of the sites of hormone manufacture in the normal organism. As new sites are discovered, for a particular hormone or group of hormones, under normal conditions, their interpretation as ectopically produced needs revision. This is apparent in the work of Buch *et al.* [6] on the newly described gastrointestinal peptide hormones and their cellular distribution: it was found that intestinal gastrin is localized in a distinct endocrine cell type different from the G cells of the antral mucosa thought the only cell responsible for this function. Also, peptides and protein hormones considered as being of pituitary origin have been detected within the central nervous system and are thought to be synthesized there. These hormones might be responsible for eliciting behavioral responses [7]. Other peptides have similarly been found in the nervous system.

Another general remark is that multiple hormones may be ectopically secreted by a single tumour. In the recent literature, reports of such multiple hormone productions are increasing in number, suggesting that this may be the rule rather than the exception. In one study [8] it was possible to recognize the presence of 8 different hormones in a single oat cell lung carcinoma: they were ACTH, BMSH, AVP, oxytocin, neurophylin, insulin, prolactin and CLIP. In this case, the ACTH production dominated the clinical picture. The other hormones produced no clinical symptoms; the concentration of the different hormones differed markedly in the primary tumour and in the liver metastases [9], a fact of interest as suggesting a biochemical heterogeneity among the cells of malignant tumours, even if morphologically similar. Another possible explanation could be the selective inactivation of certain hormones originating in the metastases by the liver.

Finally, a general remark is necessary: in certain cases, the clinical endocrine syndrome observed in a patient with a tumour should not be attributed to an ectopic hormone production, but is explained by the direct hormonal secretion of the normal endocrine gland under the influence of ectopic production by the tumour of a releasing factor-like activity [10].

All these possibilities should be kept in mind by the clinician facing a patient with a tumour and an endocrine syndrome.

3. CLINICAL SYNDROMES AND ECTOPIC HORMONE PRODUCTION

(a) *Definition*

Table 1 and Table 2 give the commonest examples of clinical syndromes produced by ectopic hormone production. It is immediately apparent that ectopic hormone secretion is not always expressed by a clinical syndrome. For instance, in lung cancer, ectopic production of ACTH produced Cushing's syndrome in 3 to 22% of cases, ADH produced antidiuresis in 8 to 35% of cases, PTH produced hypercalcemia in 6 to 16% of cases and gonadotropin

Table 1. *Some of the clinical syndromes and most characteristic tumours associated with ectopic hormone production*

Hormone	Most characteristic associated neoplasms	Syndrome
ACTH and related moeities	Oat cell bronchial carcinoma (oat cell predominantly) Islet cell carcinoma Thymic carcinoma Phaeochromocytoma and other neuroectodermal tumours Cardinoid tumour Medullary thyroid carcinoma	Cushing's syndrome
Arginine vasopressin	Bronchial carcinoma (oat cell) Carcinoid tumours	Inappropriate anti-diuresis
'PTH' and other osteolytic agents	Squamous cell carcinoma of lung Hepatoma Hypernephroma Mammary carcinoma	Hypercalcaemia
"Gonadotrophins"	Large cell carcinoma of lung Pancreatic carcinoma Gastric carcinoma Hepatoblastoma Hypernephroma	Gynaecomastia (adult males) Precocious puberty
Human placental lactogen (HPL)	Bronchial carcinoma	Gynaecomastia
Growth hormone	Bronchial carcinoma Carcinoid tumour	Hypertrophic pulmonary osteoarthropathy
Prolactin	Hypernephroma Bronchial carcinoma	Galactorrhoea
Calcitonin	Oat cell bronchial carcinoma	—
Somatomedin (NSILA)	Hepatoma Mesenchymal tumour Adrenocortical carcinoma	Hypoglycaemia
Vasoactive intestinal peptide (VIP)	Bronchial carcinoma	Watery diarrhoea and hypokalaemic alkalosis (WDHA)
Enteroglucagon	Hypernephroma	Malabsorption Constipation
Erythropoietin	Uterine carcinoma	Erythrocytosis

From [15].

produced gynecomastia only rarely [11, 12]. This may be due to several causes among which there is the possibility that the ectopic hormones, although immunologically identical with the normal hormone, have a different biological activity (vide infra ACTH) associated with small biochemical differences. It is also possible that a certain feedback mechanism is maintained in the ectopic secretion, the result of which is a low level of secretion of the hormone.

The true incidence of ectopic hormone production has been and is underestimated: factors tending to obscure the true incidence are listed below for some of the most common biochemical or clinical syndromes [9]:

(i) hypercalcemia, failure to follow up a patient for a sufficiently long time;

(ii) HPL oxytocin calcitonin, lack of a clinical syndrome in the presence of ectopic hormone production;

(iii) 'big' ACTH pro PTH, production of immunologically active but biologically inactive ectopic hormone;

(iv) α glycoprotein hormone subunits, production of a biologically inactive subunit of the hormone;

(v) GH, early death of the patient;

(vi) ACTH, operation of a normal feedback regulation suppressing ectopic hormone production;

(vii) ACTH, obscuring ADH secretion, and

Table 2. Some reported examples of multiple ectopic hormone production

Organ	Histology	Hormones
Lung	Oat cell	ACTH, PTH
	Oat cell	ACTH, AVP
	Carcinoid	ACTH, AVP, neurophysin
	Oat cell	ACTH, βMSH, CLIP, AVP, insulin, oxytocin, neurophysin, PRL
	Oat cell	Oxytocin, AVP and neurophysin
	—	Acth, βMSH, CT
	Oat cell	ACTH, βMSH, ADH
	Oat cell	ACTH, βMSH, ADH, CT
	Oat cell	ACTH, βMSH, CT
	Adenocarcinoma	ACTH, βMSH, CT
Liver	Carcinoid	ACTH, βMSH, CT
Thymus	Carcinoid	ACTH, βMSH, CT
	Carcinoid	ACTH, somatostatic, gonadotrophin releasing activity
Adrenal	Phaeochromocytoma	ACTH, βMSH, CT
Stomach	Carcinoid	ACTH, βMSH, CT
	Carcinoid	PTH, CT
	Carcinoid	ACTH, βMSH
Oesophagus	Anaplastic small cell	ACTH, βMSH CT
	Islet cell	ACTH, βMSH
Pancreas	Islet cell	PTH, CT

lack of interest of clinician or lack of laboratory facilities.

As clinicians become better informed and more aware of these possibilities, it is probable that ectopic hormone production will be recognized in the majority of patients with cancer.

(b) *Mechanisms of production of ectopic hormones*

Several authors [1, 8, 13, 14] have proposed the theory that peptide hormones evolve during synthesis storage and secretion through a cycle which has been called 'peptide cascade': such a cycle appears to occur normally in endocrine glands. It is represented as follows:

Preprohormone → prohormone →

hormone ⟨ carboxyl fragment / amino fragment

The first precursor is of high molecular weight and biologically inert. In ectopic secreting tumours, contrary to what happens in the normal endocrine gland, the progressive degradation steps are subject to variations explaining the heterogeneity of the ectopically secreted hormonal products. From the biologically active hormone are derived degradation products, carboxyl group which are generally inert and amino fragments which may be active [1].

A good example of this process is provided by the succession of events in the production of ACTH in tumours [9]. If one studies tumour extracts from a tumour secreting ACTH, they contain an excess of a peptide which is a fragment of the complete ACTH. This peptide represents the sequence 18 to 39 of the normal ACTH and is called the corticotrophin-like intermediate lobe peptide (CLIP), also found in the intermediate lobe of the pituitary; it is immunoreactive. Another fragment also found in tumour extracts is a 15 amino acid peptide. The authentic $ACTH_{1-39}$ has also been found in tumours. This example illustrates the fact that ectopically produced hormones may be different from the normal hormones, although they are usually fragments representing steps in the normal chemical evolution of the normal hormone or breakdown products of the hormones, as suggested by recent experimental the somewhat imperfect biochemical equipment of the tumour cell as compared with the normal endocrine organ.

The precursor in the peptide cascade could be common for several different peptide hormone as suggested by recent experimental work based on the injection of a messenger RNA extracted from tumours actively secreting hormones into Xenopus eggs: the precursor was found to be uniform for all hormone secreting tumours, with a molecular weight of

65,000. The suggestion was made that specific enzyme systems in each carcinoma cell were able to select the specific polypeptide hormone liberated from the common precursor [16].

(c) *Frequency of ectopic polypeptide production*

If biochemical evidence is used as the basis of the estimate of this frequency, the occurrence of ectopic hormone production is much higher than the occurrence of clinical syndromes would lead to believe. Odell *et al.* [17] call the ectopic peptide synthesis 'a universal concomitant of carcinomatous neoplasia'. Their original article should be consulted for details of methodology and measurement in human tumour extracts and blood. They studied the following peptides: ACTH and pro ACTH, β lipoprotein, human chorionic gonadotrophin, α glycopeptide chain and vasopressin–vasotocin. They found elevated levels of these peptides in over 50% of patients with untreated lung carcinoma. The most frequently found elevated was the ACTH–pro ACTH (72% while in the same group of patients hCG was found in only 7%). Similarly in a group of patients with colon carcinoma ACTH–pro ACTH was found elevated in the blood in 58% of the patients while hCG was elevated in 6%. The peptide pattern was different in lung versus colon cancer in that elevated blood BLPH concentrations were not found in colon cancer while such concentrations were frequent in lung cancer. They confirm that all peptides produced by tumours are similar or identical with peptides produced by some normal cells of the body at some time during the development of the organism, indicating that the humoral substances produced by tumours do not derive from a new (viral for instance) genetic information in the cancer cell.

(d) *Theories to explain the ectopic production of hormones by tumours*

Several theories have been proposed to explain this production.

(i) One theory is based on the derepression hypothesis; all varied morphological and functional cell types of a multicellular organism contain the identical genetic code in the nuclear acid content. Probably less than 10% of the genetic information is expressed, the remaining information is repressed or neutralized. It is suggested that a variable degree of liberation of this repressed information occurs during cell replication resulting in the programmed production of unusual (for this cell type) peptides or protein. Although mechanism of repression and derepression are not fully understood, the process of neoplastic transformation may itself modify repression controls [18].

Furthermore, it is possible that genetic data are never fully repressed or inactivated, but that in all cells variable quantities of genetic data are translated into small amounts of protein or polypeptide synthesis. If so, 'ectopic' peptide production, in small amounts, would be considered a normal cellular event associated with normal cellular proliferation but different from what occurs in neoplasia by the quantity and perhaps the quality of the produced material. Such normal production of ectopic hormone has been described for human chorionic gonadotrophin as will be discussed later. However, much experimental confirmation is necessary before this production by normal cells can be considered a general established fact. Such a confirmation should have great significance in view of the possible utilization of ectopic hormones as tumour markers useful for diagnostic or monitoring purposes. The usefulness of these markers obviously depends on their specificity for tumours, whether this specificity is quantitative or qualitative. There are objections against the explanation that ectopic hormone production is caused by random and non-random depression of the genome of the cell. This does not seem consistent with the common association of some tumour types with specific hormones, for instance ACTH and lung tumours, which suggest a non-random event. Also, the polypeptide hormones identified in ectopic hormonal production are not structurally different from those found with physiologic synthesis and secretion of the native hormone, which is against the concept of a random redepression.

(ii) Another explanation is based on the concept of the APUD cells. Pearse described a group of peptide-hormone-forming cells called APUD cells (Amine Precursor Uptake and Decarboxylation) and proposed that these cells have a common origin in the neural crest [19, 20]. These APUD cells would be the single progenitor cell type associated with peptide hormone production and their presence in all tumours producing peptide hormones could explain the similarity of ectopic hormone production by different tumours and also the syndrome of multiple ectopic hormone production. However, the common origin in the neural crest has been disputed by several workers [21–23] who think that these cells are endodermal and that the similarity of function

of the APUD cells is not necessarily correlated with a common embryonic origin.

The non-random association of hormones produced with the histological type of the tumour affords evidence for the concept. However, there are objections against it because several ectopic hormones secreted by tumours are not normally produced by APUD cells: it is the case for parathormone, renin and growth hormone, among others, and these hormones are sometimes secreted by oat cell carcinoma of the lung. In addition, there is a wide range of tumours secreting parathormone-like properties and such a wide range is not explainable by the APUD concept [24] because APUD cell type cells have not been found in all these tumours.

(iii) The cell hybridization hypothesis [25] does not seem to be able to explain all the ectopic humoral syndromes.

(iv) Therefore there is no unique hypothesis at present available to explain fully the mechanism of ectopic hormone production by tumours.

Certain authors have proposed that all tumours secreting ACTH were either tumours of endocrine glands or tumours containing endocrine-type cells. They presented impressive morphological arguments in favour of this thesis [26].

Biological significance. Apart from its potential clinical and pathological significance as a tumour marker either at the cellular or at the blood serum level, the tumour polypeptide production may have fundamental importance as expressing the secretion of a useful metabolite linked with the particular cell differentiation of the neoplastic cell. Ellison [21] has suggested that such ectopic hormone products may confer a selective advantage to the cancer cell over the normal cell, allowing it to proliferate preferentially.

There is an analogy between this production and the growth factors, also tumour products [27]. A selective advantage conferred to the cancer cell clone by a product, hormone or other, manufactured as a result of a gene modification, would imply that this product appears with a higher incidence than products not conferring a similar advantage. Since it is known that ACTH and calcitonin are found in oat cell carcinoma of the bronchus with an unusual high incidence, the suggestion has been offered that either one may confer a survival advantage to the tumour [11].

Neville and Easty [15] have recently summarized some of the perspectives on the mechanisms of cancer growth by ectopic hormone production and the growth factors recently identified in different tissues and acting on specific cell lines [27]. There are, for instance, a fibroblast growth factor, an epidermal growth factor and a somatomedin (non-suppressible insulin-like activity NSILA). All these, as well as hormonal peptides, act through the agency of specific cell membrane receptors.

It seems obvious that tumour cells capable of producing these factors ectopically should enjoy a selective advantage if they were able to respond to their presence through inappropriate growth factor receptors. Recent data [28, 29] suggest that such may be the case at least in certain types of neoplasia. For instance, a human fibrosarcoma line has been reported to produce a growth factor similar to MSA (multiplication stimulating activity), a hormone of the group of somatomedins with non-suppressible insuline activity. Tumours producing hypoglycemia and not of islet cell origin release high levels of somatomedin which could be related to tumour growth and confer growth advantage. The same authors have shown that tumour cells under certain conditions may express ectopic membrane receptors capable of responding to growth factors produced by the tumour cells themselves. This has been observed for neuroblastoma cells and phaeochromocytoma cells *in vitro.* Therefore the study of the biology of ectopic tumour products may lead to a new understanding of cancer cell proliferation by autostimulation. This concept also applies to ectopic hormones, since it has been shown that human cancer cells producing high molecular weight forms of calcitonin have receptors capable of binding the monomeric form of calcitonin. Another example of autostimulation may be found in the production of corticotrophin-like releasing activity often in association with ectopic ACTH secretion [30].

Certain authors have proposed that moieties derived from ectopic hormones produced in precursor forms be tested for growth and cell-selective advantage. In the case of big ACTH, its components tested for growth advantage conferred to the tumour are known to break down to yield a series of biologically active compounds including active ACTH, β-LPH, β-MSH, endorphins and enkephalins and they should all be tested [15].

Confirming what has been said before, the same authors have shown that extracts of all normal, non-cancerous tissues contain small quantities of immunoreactive HCTH, of β lipotropin, of α glycopeptide chain and of hCG, but always in smaller amounts than cancerous tissues. They conclude that peptide translation is not totally repressed or in-

activated in normal cells. However, the presence of the 5 peptides in abnormal amounts in the blood may be a diagnostic aid for the detection of cancer. While the production of peptides is a property of all cells, the data show that in cancer, the control of this production is lost. Similar data have been published by Ratcliffe and Podmore [31]. Obviously, studies of additional peptides in a broader variety of cancers is imperative in order to extend the concept and confirm its usefulness as a diagnostic test. Additional considerations of a general nature will be found in the following paragraphs dealing with individual syndromes.

4. INDIVIDUAL ENDOCRINE SYNDROMES

(a) *Ectopic ACTH syndrome*

Ectopic ACTH secretion is associated with MSH production and for this reason the syndrome is often called the ACTH–MSH syndrome. This has been the first recognized paraneoplasia syndrome and is one of the best studied. Excellent accounts of the discovery of the syndrome and the biochemical and clinical manifestations are found in several publications [1, 8, 13]. This was recognized by clinicians long before biochemists and biologists became interested and is a good example of the contribution of clinical medicine to basic research.

The clinical syndrome. There is a metabolic abnormality corresponding to elevated steroid levels (plasma cortisol exceeding 40 μg per 100 ml). This produces muscular wasting with weakness and occasionally diabetes and mild hypertension. The blood electrolyte abnormality is a hypokalemic alkalosis similar to that seen in advanced Cushing's disease. If the tumour is an oat cell carcinoma of the lung, in the absence of treatment, the evolution may be very rapid and the body habitus of Cushing's syndrome has no time to develop.

But if the tumour is less aggressive and is not diagnosed, the patient may be diagnosed as having the ordinary pituitary dependent Cushing's disease: this has been observed in cases of thymoma, carcinoid phaeochromocytoma or pancreatic carcinoma. Hypokalemia is an important sign which, in the absence of another cause, suggests an ectopic ACTH source. The secretion of large amounts of biologically active ACTH has been most commonly associated with carcinoma of the lung, especially the oat cell type (50% of clinical cases) [26]. There is also an elevation of androgen production and the very high levels of dehydroepiandrosterone sulfate in plasma is seen only in adrenal carcinoma and ectopic ACTH syndrome. Other tumours (see Table 1) may produce the syndrome. It has even been reported in a case of colon carcinoma [8].

Diagnosis. There are marked increases of free cortisol and adrenal androgen production seen only in adrenal carcinoma or in this syndrome. Plasma cortisol and plasma ACTH levels often exceed 40 μg% and 200 ρg/ml respectively. They are not suppressed by the administration of dexamethasone in doses which suppress plasma corticosteroids of the pituitary dependent Cushing's disease.

However, exceptions have recently been observed to this lack of suppression in the ectopic syndrome [32]. This is true especially in patients with bronchial carcinoids or with thymomas [33–35] and it has been explained by the tumour production of the corticotropin-releasing hormone (CRH), a peptide controlling pituitary ACTH secretion which is inhibited by dexamethasone while ectopic ACTH is not [10].

Venous sampling has been used to demonstrate ACTH secretion in the venous blood of the tumour and differentiate ectopic secretion from eutopic secretion [36].

The question of the relationship between plasma immunoreactive ACTH and βMSH is a complicated one in view of the artefactual nature of βMSH. This is discussed in detail by Scott, Lowry *et al.* [37, 38]. The βMSH extracted from plasma is an artefact of the methods of extraction and purification. It is split from larger peptides lipotropin (LPH) containing the entire βMSH sequence and does not exist as such in plasma.

Odell *et al.* have shown that 90% of tumour extracts from a variety of carcinoma types contain βLPH, which is also elevated in the blood of patients with untreated lung cancer without the ectopic ACTH syndrome [17]. It is not surprising that plasma and tumour ACTH and βSMH and βLPH correlate since these 2 peptides ACTH and βLPH are synthesized by the same pituitary cells. Roberts *et al.* reported that messenger RNA for ACTH directed synthesis of one large precursor molecule containing both ACTH and βLPH. This explains the hyperpigmentation observed in patients with the ectopic ACTH syndrome [39]. Ectopic ACTH secretion by benign tumours has been observed. However, in these cases, the underlying tumour usually is derived from an endocrine tissue or organ. This is the case for the benign adrenal non-catecholamine-secreting phaeochromocytoma described in [8]. The

presence in plasma of detectable ACTH not suppressed by dexamethasone is indicative of the presence of a tumour. If this was surgically removed or treated by irradiation with concomitant disappearance of the ectopic ACTH, reappearance of the hormone is a sign of recurrence of the tumour. The effect of chemotherapy of oat cell carcinoma, which has become an effective method of treatment in recent years, can also be monitored by ACTH measurements whose elevation may antedate clinical recurrence of the tumour.

(b) *Ectopic ACTH secretion without clinical expression*

There is a striking contrast between the large number of patients with oat cell carcinoma having no endocrine syndrome and the small percentage exhibiting the symptoms of hypercorticism. Even so more than half the patients with oat cell carcinoma of the lung have raised cortisol level resistant to dexamethasone administration. Significant amounts of ACTH have been found in a high proportion of lung cancer, including the non-oat cell type. This indicates that a systematic search for endocrine abnormalities should be instituted even in the absence of a clinical syndrome.

Bloomfield [40] measured ACTH concentration in 14 lung tumours from patients without the clinical syndrome. As controls they used lung tissue taken at a distance from the tumour and appearing macroscopically normal. An important observation was the discovery of levels of ACTH in the non-tumorous lung correlating well with the corresponding tumour concentration. This was interpreted as either a premalignant change or as a result of stimulation of the normal endocrine cells present throughout the lung by the tumours. Another interpretation was that the hormone secreting granules in the tumour cells might metastasize to other parts of the lung. These observations show the complexity and the many unknown factors of ectopic hormone production.

(c) *Hypercalcemia and parathormone*

Hypercalcemia is a common finding in patients with carcinoma. Yet as many as 10% do not show bone metastases. When bone metastases are present, osteolysis by the growing carcinoma is the usual explanation for the hypercalcemia usually accompanied by hyperphosphatemia in contrast to the hypophosphatemia seen in hyperparathyroidism. On the other hand, hypercalcemia without bone metastases has been reported in patients with acute myeloblastic leukemia, with hypernephroma and bronchogenic carcinoma of all histological types except perhaps oat cell carcinoma [41]. This hypercalcemia was attributed to the production by the tumour of a parathormone-like activity [42, 43] until several patients with hypercalcemia and bronchogenic carcinoma without bone metastases were described in whom no parathormone-like activity could be detected and made responsible. This hypercalcemia has been attributed to the activity of prostaglandin and this hypothesis has been supported by positive identification of prostaglandin metabolites in the urine of some hypercalcemic patients [44] and also by the occasional decrease in blood calcium when these patients were treated with indomethacin, a inhibitor of prostaglandin. However, there are contrary views on the action of prostaglandin [45] and as of now, the understanding is that hypercalcemia may be caused by a parathormone-like material or by prostaglandin. Some of the methodological difficulties inherent to the interpretation of parathyroid hormone assays are discussed in a recent paper [46]. The hypercalcemia of multiple myeloma has been attributed to an osteoclast-stimulating factor (OSF) present in extracts from myeloma cells [47].

(d) *Chorionic gonadotrophin*

The human chorionic gonadotrophin (hCG) is normally secreted by the placenta and is easily detectable in the blood during pregnancy. It is made of 2 subunits (α and β) which are dissimilar and exhibit the same quaternary structure as the three other glycopeptide hormones, TSH, LH and FSH. The different biological activities and immunological reactivities of the 4 hormones are accounted for by differences in the β subunits while the α subunits are similar or identical. Methods of detection of the hCG are based on the use of highly purified antiserum able to detect hCG specifically. Details on methodology are available in reviews by Vaitukaitis [48] and Odell [49]. Ectopic gonadotrophin secretion initially was revealed by accompanying clinical syndromes in prepubertal boys. This ectopic secretion was commonly associated with hepatoblastoma expressing itself by the appearance of precocious puberty. Lung tumours in adults have shown gynecomastia by a similar mechanism [50]. As for hCG specifically, a wide variety of tumours secrete it among which the following are listed: breast, all sections of the gastroinintestinal tract, lung, melanoma, ovary and testicle. The most elevated levels were found in

tumours of the gastrointestinal tract, sometimes exceeding levels found in pregnancy. No clinical manifestations of these levels of secretion may be apparent, perhaps because of the short duration of the exposure or for other reasons.

Large series of patients have been studied and the results are revealing: in 186 patients with carcinoma of lung and colon, approximately 25% had elevated α chain concentrations and 6% had elevated hCG concentrations [49]. It was also found in extracts of a great variety of tumours. In the study of Kahn [51], 76 patients with functioning islet-cell tumours were investigated—serum hCG, hCG and α or β chain of hCG was elevated in 63% of the 27 patients with malignant tumours and not elevated in any with benign neoplasm. These results suggest a remarkable degree of predictability for malignant tumours, but without specificity for the histological type since similar high levels are found in cancers of lung, colon or stomach.

There is also, of course, secretion of gonadotrophin by tumours of trophoblastic origin and measurement of this secretion has been used for a long time in the diagnosis and monitoring of this type of tumours. However, this does not represent an ectopic type of hormone production since the tissue of origin of the tumour normally secretes these hormones: this will not be discussed here.

The gonadotrophin secretion provides the opportunity to mention recent data indicating that perhaps malignant cell replication is commonly or universally associated with ectopic peptide production and this is particularly apparent in the case of hCG, α and β chain [49]. Recent data indicate that low but appreciable levels of the hCG are usually secreted in the normal, non-pregnant individuals: under these conditions, this secretion has been called ectopic, although the source is unknown. The significance of these observations is that secretion of hormones may not always be confined to an endocrine gland, even in the normal organisms. The hCG was especially suitable for the demonstration of this fact, since with other hormones, circulating levels are always normally present. The demonstration that one, and conceivably other, polypeptide hormones are normally secreted outside of the specific endocrine organ in the normal organism is an exciting development which may herald new interpretation of the endocrine paraneoplastic syndromes. Although other examples of other non-neoplastic ectopic hormone production are available in the literature, this one appears particularly interesting since hCG can now be considered as a normal hormonal production in non-pregnant individuals. hCG is also described in patients with a variety of non-cancerous gastrointestinal diseases, among which Vaitukaitis [48] lists regional enteritis, ulceration, colitis, cirrhosis and peptic ulcer. However, this observation was based on immunological methods without other characterization.

Recently Borkowski *et al.* have extended and confirmed these observations after extraction and purification of the human chorionic gonadotropin from the plasma proteins of healthy normal blood donors. The hormone was detected in 12 out of 16 normal subjects, of whom 13 were men. The source of the hormone is unknown, but the authors speculate that this 'ectopic' secretion of a protein hormone may be a normal phenomenon perhaps associated with rapid proliferating cells, not necessarily malignant. These observations are important as suggesting new concepts and interpretations of normal and abnormal hormone secretion [51a, b].

Of interest to the clinician is the fact that tumours secreting hCG often secrete other markers, the concentration of which vary independently. Chemotherapy may selectively suppress one of the markers, or on recurrence after remission one of the markers may not reappear; this knowledge is important to the clinician monitoring the treatment by measuring markers [49]

(e) *Growth hormone*

There have been two cases of carcinoma of the lung where some abnormality in the values of growth hormone were reported. The elevated values were not suppressed by a glucose load and in one patient the abnormality persisted after removal of the tumour [52, 53]. Growth hormone production by lung carcinoma has been invoked, without strong evidence, to explain the hypertrophic pulmonary osteoarthropathy of the secondary type which is most often accompanying lung carcinoma although other non-cancerous disease may be associated with the syndrome. The primary type of the syndrome appears after puberty and is a hereditary trait [54].

(f) *Ectopic placental lactogen*

This hormone has been found in a variety of non-trophoblastic tumours, including tumours in a man and in a non-pregnant woman [55, 56]. The lactogen has many similarities with prolactin. Its ectopic production does not seem

to be associated with a clinical syndrome. Bronchial carcinoma is the type of tumours in which it has been detected.

(g) *Calcitonin*

Calcitonin has been found in the serum of patients with oat cell carcinoma of the lung. It has also been observed in the plasma and leucocytes of patients with certain myeloproliferative disorders [57] and in 23 out of 28 patients with breast carcinoma [58] whose cell cultures released the hormone *in vitro*. It has been suggested that calcitonin secretion could be used in the staging of breast cancer. Other authors have extended the significance of ectopic calcitonin by showing the 59% of 85 tumours collected at random contained immunoreactive calcitonin [58]. These authors conclude that calcitonin is a common product of the APUD tumours and that, in their experience, ectopic calcitonin tumour production is often associated with ectopic ACTH and β melanocyte-stimulating hormone.

(h) *Hypoglycemia and cancer (somatomedin)*

Hypoglycemia is observed in a wide variety of neoplasms. These usually are not the types of tumour responsible for ectopic hormone production as described above. They are mostly mesotheliomas such as fibrosarcoma, neurofibroma, mesenchymoma, etc. The neoplasms are usually large and bulky; approximately 33% are abdominal, peritoneal and retroperitoneal [59]. The explanation of this type of hypoglycemis is not entirely known. It has been attributed to the elaboration by the tumour of a somatomedin peptide produced by the liver possibly under the stimulation of the growth hormone. When hepatoma produces somatomedin this cannot be considered an ectopic hormone production since liver is the normal organ of origin. Somatometidin has an insulin-like action ('non-suppressible insulin-like activity'). Studies by Megyesi [60] have revealed this insulin-like action in patients with a variety of carcinomas without radioimmunological evidence of the presence of insulin. However, radioimmunoassayable insulin has also been found in 2 patients with carcinoma of the cervix [61]. Nevertheless, it seems that somatometidins are probably the most frequent causes of hypoglycemia in non-pancreatic malignant tumours.

(i) *Vasoactive intestinal peptides*

Clinical syndromes produced by peptides active on the gastro-intestinal tract may not be ectopic when seen in tumours of the stomach and intestine since they are normally produced by cells of the gastrointestinal tract. The Zollinger–Ellison syndrome is caused by pancreatic tumour secretion of gastrin and resulting ulcerations of the stomach and duodenum. Whether this is an ectopic or non-ectopic secretion is debated [62]. These tumours contain gastrin and big gastrin (respectively 34 and 17 amino-acids, or 13 aminoacids); they are secreted under the influence of secretin.

Islet cell carcinoma of the pancreas and other tumours have been associated with a water diarrhea syndrome with hypokalemia and hypochlorhydria [63]. This syndrome is caused by secretion of various vasoactive products by the tumours [64].

(j) *Arginine vasopressin*

Ectopic secretion of AVP produces a syndrome characterized by hyponatremia, hypervolemia, high urine osmolality and high urine sodium concentration. It is seen mostly in carcinoma of the lung of all histological types, but has occurred in association with carcinoma of the prostate and Hodgkin's disease [65, 66]. According to Gilby *et al.* [67] 40% of oat cell carcinomas are associated with inappropriate argine vasopressin secretion. This can be identified by radioimmunoassay and is identical with the normally secreted AVP [47]. The syndrome is clinically and biochemically demonstrable in many patients, especially if given excess water. Water should be restricted in these patients. Recently a similar syndrome has been described in carcinoma of the bladder [68]. The production of an identical syndrome has been also attributed to the administration of vincristine, endoxan and other chemical agents.

(k) *Multiple hormone production by a single tumour*

We have already alluded to this phenomenom in the introduction. Examples of this occurrence have been re-emphasized in the recent literature. An islet cell tumour of the pancreas was described [69, 70] which, in addition to insulin, secreted glucagon, serotonin, ACTH, βMSH, gastrin and a secretin-like hormone. The association of these diverse active polypeptides occasionally cause the appearance of bizarre syndromes which are difficult to diagnose if the cause, a malignant tumour, is not recognized. Such unusual associations of endocrine abnormalities should suggest the diagnosis of cancer. Other recent examples of multiple hormone ectopically and eutopically produced are found in the observation of an adrenocortical carcinoma with three major endocrine abnormalities attributable directly to the

tumour: hypercortisolism (Cushing's syndrome), hyperoestrogenism (feminization) and hypercalcemia (pseudohyperparathyroidism) with normal parathyroid glands at autopsy [71]. Well documented cases of multiple ectopic hormone production have been described for prostatic cancer [72] and small carcinoma of the lung [73]. Easty and Neville have listed some reported examples of multiple ectopic hormone production (Table 2).

5. OTHER ABNORMALITIES ASSOCIATED WITH THE PRESENCE OF TUMOURS

There are several syndromes associated with the hyperactivity of tumoral tissue in secreting the normal secretory products of the tissue of origin. These are not ectopic secretions since they reflect the activity of the normal tissue from which the tumour originated. The increased production of secretory products by the tumour is not so much the result of the increased volume of secreting tissue as the loss or alteration of the feedback mechanism which regulates the normal secretion by normal tissue. This explanation results from the consideration that in normal circumstances there is always a considerable excess of secreting tissue as compared to the amount of product needed even under extreme demand. Regulatory mechanisms maintain a normal secretion and this is what appears to be altered when a tumour secreting the normal product of the gland does so in an inappropriate way.

(a) *Erythrocytosis*

An example of this is provided by the erythrocytosis associated with renal tumours (approximately 5%) and, rarely, liver tumours. Normally, the kidney is the usual site of erythropoietin production but other tissues, particularly the liver, respond to severe hypoxia by secreting erythropoietin [74, 75]. In renal tumours, the erythrocytosis represents an excess production of the normal product of the tissue from which the tumour arises. Cerebellar hemangioblastoma is another tumour associated with polycytemia [76]: erythropoietin has been isolated from cerebellar cysts in these cases. Polycytemia has also been observed in adrenal cortical tumours producing androgens. These are able to sensitize the erythrocyte population to the proliferating action of erythropoietin [77]. These types of polycytemia are not associated with a decreased arterial oxygen saturation and may be difficult to distinguish from polycytemia vera. Erythropoietin in increased amounts can be demonstrated in the blood and urine. The polycytemia disappears with eradication of the responsible tumour.

(b) *Blood plasma defibrination*

The first report of defibrination with fibrinolysis associated with disseminated cancer was reported in 1952 [78] and additional cases, showing the frequency of the syndrome, were reported in 1953 [79]. A study of fluctuating fibrinogen levels and other coagulation factors over a period of observation of 150 days in a patient with cancer of the prostate [80] showed that these manifestations were closely associated with periodic growth, and regression of the cancer induced by oestrogen treatment. Such defibrination has been produced experimentally in dogs by the injection of trypsin and thrombin [81]: this syndrome of defibrination has been since described in innumerable articles, and found associated with cancer or noncancerous conditions. Evidence has been forthcoming that defibrination may be caused by intravascular coagulation with or without accompanying fibrinolysis, or to primary fibrinolysis not necessarily associated with intravascular coagulation. Direct fibrinogenolytic and fibrinolytic activity have been demonstrated in the human prostate, both in adenoma and prostatic cancer [80]: therefore defibrination could be caused by the internal prostatic secretion. The question of the mechanism of production of this type of hemorrhagin diathesis in cancer is still under advisement [3]. It should be noted that intravascular coagulation and fibrinolysis could coexist without being casually related since the same intracellular tissue fraction contains activators of plasminogen [82].

(c) *Carcinoid tumours*

Carcinoid tumours produce the well known carcinoid syndrome characterized by flushing, diarrhoea and occasional wheezing respiration. Right sided heart failure was sometimes observed accompanied by right sided valvular defects and thickening of the endocardium of the right heart. The carcinoid tumours originating in the argentaffin tumours of the intestinal wall are often benign, but the malignant forms metastasize in the lymph nodes and the liver. Liver metastases from intestinal tumours appear to be necessary for the production of the syndrome.

This is explained by the secretion of 5-HT in increased amounts in the blood. This compound is formed from 5-hydroxythryptophane and broken down to 5 HI AA, whose detection is important for the diagnosis. The outflow of tumour products should be directly into the

heart in order to produce the syndrome. Besides metastases in the liver, this condition is fulfilled by carcinoid tumours of the bronchi or of ovarian teratomas draining into the vena cava. Serotonin is inactivated by passage through the lung and this probably explains why the left side of the heart is not affected. This carcinoid syndrome is extensively and clearly described and analyzed in the monograph of Waldenström, who has been the main contributor to the discovery and knowledge of this syndrome [3].

(d) *Medullary thyroid carcinoma*

This is a histologically undifferentiated tumour containing large amounts of amyloid. This tumour produces calcitonin, as does the tissue of origin represented by cells normally found in the thyroid gland. These tumours occur often in association with other tumours, such as pheochromocytoma, mucosal neuroma, etc. These tumours may have a good prognosis and calcitonin blood levels should be monitored for diagnosis and surveillance of treatment [83].

(e) *Pheochromocytoma*

These tumours originate from cells of the autonomous nervous system and in the blast form are the neuroblastoma. These are very malignant and their cells do not contain granules. Pheochromocytomas secrete catecholamines which produce hypertension and an elevated basal metabolism. The measurement of catechloamines and metabolites in the urine is important for the diagnosis of pheochromocytoma and also (see below) for neuroblastoma: neuroblastoma patients do not excrete epinephrine but do excrete norepinephrine [3].

6. BIOCHEMICAL MARKERS FOR DIAGNOSIS, LOCALIZATION AND MONITORING OF CANCER

Ectopic hormones serve to some extent as indicators of the presence of a tumour. But by and large so far their detection and measurement have not been useful for the diagnosis because the tumour is clinically apparent before they are detected. The exact correlation between size of the tumour and appearance of ectopic hormones is not known. Obviously their detection either in the blood or by the hormonal syndrome they produce should precede the clinical manifestations of the tumour growth if the purpose of early diagnosis is to be served. It is conceivable that further methodological refinement in the biochemical tracing of very small amounts of ectopically produced hormone may some day contribute to early diagnosis of cancer, this means the diagnosis of cancer well ahead of its clinical appearance.

However, present methods based on radioimmunoassays are already measuring amounts of hormones so small that this achievement was inconceivable 10 to 15 years ago. The value of ectopic markers (not reviewed here) such as hCG and its subunits for gestational choriocarcinoma, *αFP* for hepatomas or yolk sac carcinomas, calcitonin and medullary carcinoma, steroid hormones and adrenocortical tumours is well recognized and routinely employed in the diagnosis and treatment of these specific types of tumours [83].

There are other markers which are not hormones and are diversely related to the presence of certain types of tumours, do not produce clinical syndromes and probably do not properly belong to this review. However, they should be mentioned here for the sake of completeness and because they represent a field of investigation which holds promise for the future of the early detection of cancer. However, no definite results have been obtained so far and this field should still be considered as being at the experimental stage. There have been several general reviews of biological cancer markers which should be consulted for a detailed discussion of the subject presented below in summarized form [3, 84, 85].

(a) *Carcinoembryonic antigen*

Carcinoembryonic antigen (CEA) originally was identified by means of a heterologous antiserum prepared against colon carcinoma extracts and purified by absorption with normal extracts. The early hope was that detection of CEA would be specific for colon cancer but it was soon found that abnormal high levels of CEA were found in the blood of patients with a wide variety of tumours as well as non-malignant diseases and after blood transfusion. Improvement in the purification of the CEA antigen may in the future increase the accuracy of the test. Clinical studies with CEA have been published recently [86, 87]. There are 2 clinical situations in which monitoring CEA has usefulness, namely the follow-up of patients with colo-rectal cancer and the prognostication of patients treated for breast carcinoma. However, Moertel *et al.* [88] denied that CEA is adequate for detecting early recurrence of treated carcinoma. Neville stated that CEA can help in the detection of tumour dissemination but has little value for the prognostic

stratification of stage I and II of breast cancer. There are, of course, many other methods besides the uncertain CEA determination, to detect and define dissemination of breast cancer [89]. Therefore CEA should be considered at present as an experimental diagnostic test, still in need of much improvement and refinement to acquire specificity and safety. As of now it has limited usefulness for monitoring the results of treatment and the early detection of recurrence of treated tumours. Interest of the clinicians in this type of diagnostic methods will constitute a stimulus for the pursuit of biochemical and biological research in this field.

(b) *Alpha foetoprotein* (αFP)

This is the first globulin to appear in mammalian serum in early embryonic and foetal life with a maximum level in humans at 12–14 weeks of foetal age. The adult level is very low, at 10–15 mg/ml. The detection and measurement of this antigen in adults has been of help in the diagnosis and follow up of patients with hepatoma and germ cell tumours [86, 87].

(c) *Leukemia cell markers*

Leukemia cells in humans are considered heterogenous despite a similar histological appearance. By means of immunological, enzymatic and chromosomal studies, great progress has been made in identifying several subgroups of leukemia with different prognoses and different therapeutic indications. For details of this very specialized field, the reader is invited to consult the general reviews in this bibliography [83].

(d) *Miscellaneous*

There are several other markers at present under study, none of which has attained the level of clinical usefulness. However, there is no question that this type of study is absolutely essential for the improvement of our possibilities of early detection of cancer.

7. CONCLUSION

The discovery of ectopic hormone production by neoplasms was made by clinicians long before biologists and biochemists became interested in the subject. However, the progress of biochemical methods for the measurement of minute amounts of hormone almost due entirely to the ratioimmunoassays has led to impressive development of the subject of hormonal paraneoplastic syndromes.

This field is of great interest to the clinician in general and particularly the oncologist. It is important that he should keep himself informed of the evolution of the discoveries because clinical application of the advances in this field will probably become an essential contribution to the diagnosis of cancer in the near future. In the presence of the very unsatisfactory present state of the diagnosis of cancer at an early stage, this new biochemical approach may represent our hope for a real early diagnosis based on detectable biochemical abnormalities in body fluids appearing well before the cancer reaches the presently recognizable size. Increasing collaboration between clinicians and biochemists particularly in cancer centers, and the extension to large series of patients of the techniques developed in the research laboratory, are necessary for rapid progress in this important area of cancer control.

The clinical syndromes present another interest for the clinicians. They are markers and can be used in diagnosis and treatment. The presence of clinical syndrome will suggest the diagnosis of cancer to the informed clinician. From now on this diagnostic possibility should always be kept in mind and verified in every patient with an endocrine abnormality, especially when it is unusual, as is the case for the multiple ectopic hormone production.

Finally, the presence of polypeptides on the cancer cell membrane, considered by certain authors as a universal characteristic of malignant tumours, opens new possibilities of therapeutic approaches since these peptides may be indispensable for the growth of the cancer and their neutralization or inactivation may seem to be within the capabilities of present day medical science.

REFERENCES

1. ODELL WD, WOLFSEN AR. Humoral syndromes associated with cancer. *A Rev Med* 1978; **29**: 379–406.
2. NEVILLE AM, SYMINGTON T. Systemic factors produced by human neoplasms. In AMBROSE EJ, ROE FJC. eds. *Biology of Cancer*. Chichester: Ellis Horwood, 1975: 126–144.
3. WALDENSTRÖM JG. *Paraneoplasia. Biological Signals in the Diagnosis of Cancer*. London: Wiley and Sons, 1978.
4. REES LH. Hormone production by tumours. *Antibiot Chemother* 1978; **22**: 161–165.

5. VAITUKAITIS JL. Peptide hormones as tumor markers. *Cancer* 1976; Jan. Suppl. 567–572.
6. BUCHAN AMJ, POLAK JM, SOLCIA E, PEARSE AGE. Localisation of intestinal gastrin in a distinct endocrine cell type. *Nature (Lond)* 1979; **277**: 138–140.
7. KRIEGER DT, LIOTTA AS. Pituitary hormones in brain: where, how, and why? *Science* 1979; **205**: 366–372.
8. REES LH, BLOOMFIELD GA, REES GM. Multiple hormones in a bronchial tumour. *J Clin Endocrinol Metab* 1974; **38**: 1090–1097.
9. REES LH. The biosynthesis of hormones by non-endocrine tumours. A review. *J Endocrinol* 1975; **67**: 143–175.
10. SHALET SM, BEARDWELL CG, MCFARLANE IA, ELLISON ML, NORMAN CM, REES LH, HUGHES M. Acromegaly due to production of a growth hormone releasing factor by a bronchial carcinoid tumour. *Clin Endocrinol* 1979; **10**: 61–67.
11. GEWIRTZ G, YALOW RS. Ectopic ACTH production in carcinoma of the lung. *J Clin Invest* 1974; **53**: 1022–1023.
12. NEVILLE AM, GRIGOR KM, HEYDERMAN E. Biological markers and human neoplasia. In ANTONY PP, WOOLF N. eds. *Recent Advances in Histopathology.* Edinburgh: Churchill Livingstone, 1900: Vol. 10, 23–52.
13. REES LH, BLOOMFIELD GA, GILKES JJH, JEFFCOATE WJ, BESSER GM. ACTH as a tumor marker. *Ann N.Y. Acad Sci* 1977; **297**: 603–620.
14. BLACKMAN MR, ROSEN SW, WEINTRAUB BD. Ectopic hormones. *Adv Intern Med* 1978; **23**: 85–113.
15. NEVILLE AM, EASTY GC. Ectopic polypeptide production by tumours. *Rev Endocrinol Related Cancer* 1979; **3**: 25–32.
16. LIPS CJM, VAN DER SLUYS VEER J, VAN DER DONK JA, VAN DAM RH, HACKENG WHL. Common precursor molecule as origin for the ectopic-hormone-producing-tumour syndrome. *Lancet* 1978; 16–18.
17. ODELL WD, WOLFSEN AF, YOSHIMOTO Y, WEITZMAN R, FISHER DA, HIROSE F. Ectopic polypeptide synthesis: a universal concomitant of neoplasia. *Trans Ass Am Phys* 1977; **90**: 204–227.
18. WATSON JD. *Molecular Biology of the Gene,* 3rd Edn. Amsterdam: W. A. Benjamin 1977: 397–418.
19. PEARSE AGE. Common cytochemical properties of cells producing polypeptide hormones, with particular reference to calcitonin and the thyroid C cells. *Vet Rec* 1966; **79**: 587–590.
20. PEARSE AGE. The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the Apud series and the embryologic and pathologic implications of the concept. *J Histochem Cytochem* 1969; **17**: 303–313.
21. ELLISON ML, NEVILLE AM. Neoplasia and ectopic hormone production. In: RAVEN RW. ed. *Modern Trends in Oncology. Part I.* London: Butterworths, 1963: 163–181.
22. ANDREWS AJ. A study of the developmental relationship between enterochromaffin cells and the neutral crest. *J Embryol Exp Morth* 1963; **11**: 307–320.
23. LE DOUARIN N. Personal communication. 1972. In: AMBROSE EV, ROE FJC. eds. *Biology of Cancer.* Chichester: Ellis Horwood, 1976.
24. VISSER PA, FRIESEN SR. Uncommon tumors of the APUD system. *Surg Clin North Am* 1979; **59**: 143–158.
25. WARNER TFCS. Cell hybridation in the genesis of ectopic hormone secreting tumours. *Lancet* 1974; 1259–1260.
26. AZZOPARDI JG. WILLIAMS ED. Pathology of non endocrine tumors associated with Cushing's syndrome. *Cancer* 1968; **22**: 274–286.
27. GOSPODAROWICZ D, MORAN RS. Growth factors in mamalian cell culture. *A Rev Biochem* 1976; **45**: 531–558.
28. TODARO GJ, DE LARCO SP, NISSLEY G, RECHLER MM. MSA and EGF receptors on sarcoma virus transformed cells and human fibrosarcoma cells in culture. *Nature (Lond)* 1977; **267**: 526–528.
29. DE LARCO JE, TODARO GJ. A human fibrosarcoma cell line producing multiplication stimulating activity (MSA)-related peptides. *Nature (Lond)* 1978; **272**: 356–358.
30. HAM J, WILLIAMS JC, ELLISON ML. Radioreceptor assay for the detection of biologically active forms of calcitonin. *J Endocrinol* 1979; **81**: 152–153.
31. RATCLIFFE JC, PODMOREJ. Ectopic hormones. In: SYMINGTON Th, WILLIAMS AE, MCVIE JG, eds. *Cancer Assessment and Monitoring.* Churchill Livingstone, 1980.
32. REES LH. Concepts in ectopic hormone production. *Clin Endocrinol* 1976; 5 (suppl.) 3635–3725.

33. MASON AMS, RATCLIFFE JG, BUCKLY RM, MASON AS. ACTH secretion by bronchial carcinoid tumors. *Clin Endocrinol* 1972; **1**: 3–25.
34. UPTON GV, AMATRUDA TT, Jr. Evidence for the presence of tumor peptides with corticotropin-releasing-factor-like activity in the ectopic ACTH syndrome. *N Engl J Med* 1971; **285**: 419–424.
35. YAMAMOTO H, HIRATA Y, MATSUKURA S, IMURA H, NAKAMURA M, TANAKA A. Studies on ectopic ACTH-producing tumors. IV: CRF-like activity in tumour tissue. *Acta Endocrinol* 1976; **82**: 183–192.
36. CORRIGAN DF, SCHAAF M, WHALEY RA, CZERWINSKI CL, EARLL JM. Selective venous sampling to differentiate ectopic ACTH secretion from pituitary Cushing's syndrome. *N Engl J Med* 1977; **296**: 861–862.
37. SCOTT AP, LOWRY PJ. Adrenocorticotrophic and melanocyte-stimulating peptides in the human pituitary. *Biochem J* 1974; **139**: 593–602.
38. BLOOMFIELD GA, SCOTT AP, LOWRY PJ, GILKES JJH, REES LH. A reappraisal of human βMSH. *Nature* 1974; **252**: 492–493.
39. ROBERTS JL. *Endocrinol Soc Progr 59th Annual Meeting* 1977; 75.
40. BLOOMFIELD GA. ACTH-secreting lung tumours. *Clin Endocrinol* 1977; **6**: 95–104.
41. BENDER RA, HANSEN H. Hypercalcemia in bronchogenic carcinoma. A prospective study on 200 patients. *Ann Intern Med* 1974; **80**: 205–208.
42. LIPSETT MB, ODELL WD, ROSENBERG LE, WALDMANN TA. Humoral syndromes associated with non-endocrine tumors. *Ann Int Med* 1964; **61**: 733–756.
43. RATCLIFFE JG, REES LH. Clinical manifestations of ectopic hormone production. *Br J Hosp Med* 1974; **11**: 685–692.
44. SEYBERTH HW, SEGRE GV, MORGAN JL, SWEETMAN BJ, POTTS JT, OATES JA. Prostaglandins as mediators of hypercalcemia associated with certain types of cancer. *N Engl J Med* 1975; **293**: 1278–1283.
45. TASHJIAN AH, Jr. Prostaglandins, hypercalcemia and cancer. *N Engl J Med* 1975; **293**: 1317–1318.
46. RAISZ LG, YAJNIK CH, BOCKMAN RS, BOWER BF. Comparison of commercially available parathyroid hormone immunoassays in the differential diagnosis of hypercalcemia due to primary hyperparathyroidism or malignancy. *Ann Intern Med* 1979; **91**: 739–740.
47. MUNDY GR, RAISZ LG, COOPER RA, SCHECHTER GP, SALMON SE. Evidence for the secretion of an osteoclast-stimulating factor in myeloma. *N Engl J Med* 1974; **291**: 1041–1046.
48. VAITUKAITIS JL. Glycoprotein hormones and their subunits. *Recent Prog Hormone Res* 1976; **22**: 295–317.
49. ODELL WD. Glycopeptide hormones and neoplasms. *N Engl J Med* 1977; **11**: 609–610.
50. ROSE LI, WILLIAMS GH, JAGGER PI, LAULER DP. Feminizing tumor of the adrenal gland with positive chorionic-like gonadotropin test. *J. Clin Endocrinol Metab* 1968; **28**: 903–908.
51. KAHN CR, ROSEN SW, WEINTRAUB BD, FAJANS SS, GORDEN P. Ectropic production of chorionic gonadotropin and its subunits by islet-cell tumors. A specific marker for malignancy. *N Engl J Med* 1977; **297**: 565–569.

51. a. DOSOGNE-GUERINF M, STOLARCZYK A, BORKOWSKI A. Prospective study of the α and β subunits of human chorionic gonadotrophin in the blood of patients with various benign and malignant conditions. *Eur J Cancer* 1978; **14**: 525–532.

51. b. BORKOWSKI A, MUQUARDT C. Human chorionic gonadotropin in the plasma of normal, nonpregnant subjects. *N Engl J Med* 1979; **301**: 298–302.

52. DUPONT B, HØYER I, BORGESKOV S, NERUP J. Plasma growth hormone and hypertrophic osteoarthropathy in carcinoma of the bronchus. *Acta Med Scand* 1970; **188**: 25–30.
53. GREENBERG PB, BECK C, MARTIN TJ, BURGER HG. Synthesis and release of human growth hormone from lung carcinoma in cell culture. *Lancet* 1972; **i**: 350–352.
54. SCULLY RE, GALDABINI JJ, MCNEDY MU. Weekly clinicopathological exercises: Case 38–1978. *N Engl J Med* 1978; **299**: 708–714.
55. WEINTRAUB BD, ROSEN SW. Ectopic production of human chorionic somatomammotropin by nontrophoblastic cancers. *J. Clin Endocrinol Metab* 1971; **32**: 94–101.
56. GASPARD U, HENDRICK JC, REUTER AM, FRANCHIMONT P. Dosage radioimmunologique de l'hormone chorionique somatomammotrope humaine (HCS) par les immunoadsorbants-anticorps. *Ann Biol Clin* Paris 1973; **31**: 447–454.

57. Hillyard CJ, Oscier DG, Foa R, Catovsky D, Goldman JM. Immunoreactive calcitonin in leukaemia. *Br Med J* 1979; **2**: 1392–1393.
58. Coombes C, Easty GC, Detre SI, Hillyard CJ, Stevens U, Girgis SI Galante S, Heywood L, MacIntyre I. Secretion of immunoreactive calcitonin by human breast carcinomas. *Br Med J* 1975; **4**: 197–199.
59. Odell WD. Humoral manifestations of non-endocrine neoplasms. In Williams RH. ed. *Textbook of Endocrinology*, 5th Edn. Philadelphia: Saunders, 1974: 1105–1116.
60. Megyesi K, Kahn CR, Roth J, Gordon P. Hypolgycemia in association with extrapancreatic tumors: demonstration of elevated plasma NSILA-S by a new radioeceptor assay. *J Clin Endocinol Metab* 1974; **38**: 931–934.
61. Kiang DT, Bauer GE, Kennedy BJ. Immunoassayable insulin in carcinoma of the cervix associated with hypoglycemia. *Cancer* 1973; **31**: 801–804.
62. Mitschke H. Pathomorphologic studies of the endocrine cell in the gastrointentinal mucosa. Physiology, cytochemistry and ultra structure. *Morphol Pathol* 1977; **104**: 1–203.
63. Kahn CR, Levy AG, Gardner JD, Miller JV, Gorden P, Schein PS. Pancreatic cholera: Beneficial effects of treatment with streptozotocin. *N Engl J Med* 1975; **292**: 941–945.
64. Gagel RF, Costanza ME, Delellis RA, Norton RA, Bloom SR, Miller HH, Ucci A, Nathanson L. Streptozotocin-treated Verner–Mossison syndrome: plasma vasoactive intestinal peptide and tumor responses. *Arch Intern Med* 1976; **136**: 1429–1435.
65. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967; **42**: 790–806.
66. Cassileth PA, Trotman BW. Inappropriate antidiuretic hormone in Hodgkin's disease. *Am. J Med Sci* 1973; **265**: 233–235.
67. Gilby ED, Rees LH, Bondy PK. Proceedings of the 6th International Symposium on Biological Characteristics of Human Tumours. In: Davis W, Maltoni C, Burch PRJ, eds. *Advances in Tumour Prevention, Detection and Characterization.* Amsterdam: Elsevier, 1976: Vol. 3, 132.
68. Kaye SB, Ross EJ. Inappropriate anti-diuretic hormone (ADH) secretion in association with carcinoma of the bladder. *Postgr Med J* 1977; **53**: 274–276.
69. Zollinger RM, Mazzaferri EL. Tumors of the islets of Langerhans. *Adv Surg* 1976; **10**: 137–176.
70. Larsson LI. Endocrine pancreatic tumors. *Hum Pathol* 1978; **9**: 401–416.
71. Deasis DN, Jr, Samaan NA. Feminizing adrenocortical carcinoma with Cushing's syndrome and pseudohyperparathyroidism. *Arch Intern Med* 1978; **132**: 301–303.
72. Wenk RE, Bhagavan BS, Levy R, Miller D, Weisburger W. Ectopic ACTH, prostatic oat cell carcinoma and marked hypernatremia. *Cancer* 1977; **40**: 773–778.
73. Hirata Y, Matsukura S, Imura H, Yakura T, Ihjima S, Nagase C, Itoh M. Two cases of multiple hormone-producing small cell carcinoma of the lung. Coexistence of tumor ADH, ACTH and βMSH. *Cancer* 1976; **38**: 2575–2582.
74. Schooley JC, Mahlmann LJ. Extra renal erythropoietin production by the liver in the weanling rat. *Proc Soc Exp Biol Med* 1974; **145**: 1081–1083.
75. Peschle C, Rapport IA, Jori GP, Ghiariello M, Gordon AS, Condorelli M. Sustained erythropoietin production in nepthrectomized rats subjected to severe hypoxia. *Br J Haematol* 1973; **25**: 187–193.
76. Valentine WN, Hennessy TG, Lang E, Longmire R, McMillan R, Odell W, Ross JF, Scott JL, Simmons DH, Tanaka KR. Polycythemia: erythrocytosis and erythermia. *Ann Intern Med* 1968; **69**: 587–606.
77. Singer JW, Samuels AI, Adamson JW. Steroids and erythropoiesis: *in vitro* evidence of different target cells for etiocholamolane and fluoxy mesterone. *Proc 17th Annual Meeting Am Soc Haematol*, 1974; 46.
78. Keffer JJ, Watts NB. *Modern Solutions to Common Endocrinologic Problems.* Asheville, NC: Precision Diagnostic Press 1975: 23–24.
79. Tagnon HJ, Whitmore WF, Schulman P, Kravitz SC. The significance of fibrinolysis occuring in patients with metastatic cancer of the prostate. *Cancer* 1953; **6**: 63–67.
80. Tagnon HJ. The nature of the mechanism of the shock produced by the injection of trypsin and thrombin. *J Clin Invest* 1945; **24**: 1–10.
81. Gordon PR, Huvos AG, Strong EW. Medullary carcinoma of the thyroid gland. *Cancer* 1973; **31**: 915–924.
82. Nijs M, Brassine C, Coune A, Tagnon HJ. Interaction des facteurs tissulaires et sanguins dans les coagulopathies de consommation et de fibrinolyse. *Bulletin de l'Académie Royale de Médecine de Belgique*, VIIe série, 1967; **7**: 643–600.

83. BOELSMA E, KROES R, RUMKE P. Eds. *Tumour Markers, Impacts and Prospects.* Amsterdam: Elsevier, 1979.
84. BONADONNA G, MATHE G, SALMON SE. Ed. Markers and General Problems of Cancer Adjuvant Therapies. *Recent Res Cancer Res* Vol. 67, 1979.
85. Proceedings of the First International Conference on the Clinical Uses of Carcinoembryonic Antigen. 1–3 June, 1977, Lexington, Kentucky. *Cancer* 1977; **42**: 1397–1659.
86. KREBS B, LALANNE CH, SCHNEIDER M. Ed. Clinical applications of carcinoembryonic antigen and other antigenic markers assay. *Excerpta Medica Intern Congress Series*, No. 439, 1978.
87. LEHMANN FG. Ed. *Carcino-embryonic Proteins.* Amsterdam: Elsevier, 1979 Vol. I and II.
88. MOERTEL CG, SCHUTT AJ, GO VLM. Carcinoembryonic antigen test for reccurrent colorectal carcinoma. Inadequacy for early detection. *J Am Med Ass* 1978; **239**: 1065–1066.
89. WANG DY, BULBROOK RD, HAYWARD JL, HENDRICK JC, FRANCHIMONT P. Relationship between plasma carcinoembryonic antigen and prognosis in women with breast cancer. *Eur J Cancer* 1975; **11**: 615–618.

II. Neurological Paraneoplasia

J. HILDEBRAND

THE MECHANISM or mechanisms by which remote effects of cancer may produce lesions of the nervous system is the most poorly understood domain of the paraneoplastic diseases. Before considering the difficult problem of the relationship between malignancy and different disorders of the nervous system one has to stress the great variety of diseases attributed to the remote effects of cancer. A guide for their classification, based on clinicopathological features, was first provided by Brain and Adams [1]. We have recently reviewed the clinical and pathological characteristics of these disorders [2], and these are only briefly summarized in Table 1.

As already mentioned, the pathogenesis of the carcinomatous neuropathies remains poorly understood. It is unlikely that the etiology of such a heterogeneous group of diseases is unique, and therefore it is not surprising that several mechanisms have been considered.

1. PRODUCTION OF HORMONES, PROTEIN, OR OTHER SUBSTANCES BY NEOPLASTIC CELLS

Neurological disorders due to abnormal and excessive production of hormones by tumour cells represent truly paraneoplastic syndromes which may be cured by the removal of neoplasia. These neurological disorders are usually associated with oat cell lung carcinomas and consist of metabolic encephalopathies which may be due not only to an abnormal production of hormones but also to other, less specific causes related to cancer (Table 2).

A rare clinical condition characterized by disturbed consciousness is encountered in hyperviscosity syndrome due to an excessive production of protein by tumour cells. The syndrome is more common in macroglobulinemia that in myeloma, where impairment of consciousness is more likely to be related by hypercalcemia [3].

The last example of a disorder which is certainly caused by the release of active substances by the tumour cells is the carcinoid-syndrome myopathy [4]. This very rare condition is due to the production of serotonin and possibly also of histamine or kalliterine. These products are able to reach the systemic circulation only when the digestive carcinoid tumours produce liver metastases or when they arise outside the digestive tract. It should be pointed out that in rats serotonin causes muscle weakness which may be prevented by antiserotonin drugs, if they are given prior to serotonin administration [5].

In all other forms of carcinomatous neuropathies, the production by the tumour of substances responsible for the remote effect of cancer on the nervous tissue remains speculative. Generally there is no correlation between the response to treatment of the neuropathy and that of the underlying malignancy, and no correlation between the extent of the neoplasm and the severity of the neurological disease. The relationship between the so-called carcinomatous neuropathies and cancer is there-

Table 1. Classification and features of carcinomatous neuropathies

Syndrome	Relative frequency as carcinomatous neuropathy	Main clinical signs	Pathology		Main associated neoplasia
			Location	Type of lesions	
Metabolic encephalopathies	frequent	Mental changes Alteration of consciousness			Various Oat cell lung carcinoma when caused by production of hormones by the tumour
Opsoclonus	very rare	Lightning and chaotic eye movements	Cerebellum (?) Brain stem (?)		Neuroblastoma
Diffuse polyencephalomyelitis	rare	Rapidly progressive dementia Ophtalmoplegia, nystagmus, bulbar palsies.	Limbic system Brain stem	Widespread Lymphoctic inflammatory reaction	Lung carcinoma main oat cell
	—	Limb weakness muscle atrophy	Ventral horns of spinal cord	Less striking neuronal degeneration	Mainly oat cell
Subacute cerebellar degeneration	may be	Ataxia, dysarthria, nystagmus	Cerebellar cortex	Disappearance of Purkinje cells. Very mild inflamatory reaction	Less commonly
Sensory neuropathy of Denny–Brown	associated	Involves lower limbs: paresthesia, sensory changes and ataxia	Root ganglia and spinal cord	Destruction of cells Inflamatory reaction Declination of spinal tracts	Ovary and breast carcinoma
Amyotrophic lateral sclerosis	very rare	May be associated with diffuse polyencephalomyelitis Weakness amyotrophy, fasciculations Pseudobulbar palsy, spasticity, Babinski sign	Low motor neuron corticobulbar and corticospinal tracts	Degeneration	Lung carcinoma

Necrotizing myelopathy	very rare	Acute or subacute paraplegia	Predominently at thoracic spinal level	Massive or patchy necrosis of the grey and white matter	Lung carcinoma
Sensorimotor peripheral neuropathy	frequent	Parastesia, depression of reflexes, distal weakness and amyotrophy, sensory changes	Peripheral nerves	Axonal degeneration	Lung and breast carcinomas
Eaton–Lambert syndrome	fairly rare	Proximal limb (mainly lower) weakness Fatigue relieved by repetition of movements Characteristic electromyography	Neuromuscular junction	Reduction of acetyl choline vesicles in motor nerve endings	Oat cell lung carcinoma
Neuromyopathy	the most common	Proximal weakness of body-supporting muscles Depression of tendon reflexes	Proximal limb (mainly lower) muscles Peripheral nerves (?)	Lesions of muscle fibers with inflamatory cell infiltration	Mainly lung and breast carcinomas
Polymyositis and dermatomyositis	fairly rare	Proximal muscular weakness with spontaneous remissions and exacerbations Muscle tenderness and pain Dermatitis	Muscles	Focal or diffuse necrosis of muscle fibers, regenerative activity and inflamatory reaction	Lung, breast and ovary carcinomas Lymphomas
Myopathy of carcinoid syndrome	very rare	Progressive proximal weakness plus general symptoms of carcinoid syndrome	Muscles	Atrophy and necrosis	Serotonin-secreting tumours (arising from intestine argentaffin cells)

Table 2. Main causes of metabolic encephalopathies in patients with cancer

Metabolic abnormalities	Paraneoplastic syndromes, tumor secretion of	Other causes related to cancer
Hypercalcemia	Parathormone; parathormone-like substance, prostaglandine E	Bone metastases; multiple myeloma
Hypokalemia	ACTH	Malabsorption due to carcinomatous or postradiation lesions of mesenteric lymphatics
Hypernatremia	ACTH	Hemoconcentration
Hypernatremia	ACTH	Hemoconcentration
Hyponatremia	Antidiuretic hormone (Schwartz–Barter syndrome)	Vincristine and cyclophosphamide treatment
Hypoglycemia	Insulin, insulin-like hormone	Glucose consumption by the tumour (?)
Uremia	—	Nephrotoxic chemotherapy (methotrexate), obstruction of urinary tract by tumour
Anoxia	—	Pulmonary primary and metastatic tumours; pulmonary infection, anemia
Hepatic failure	—	Liver primary and metastic tumours; Hepatoxic chemotherapy (I-asparaginase)

fore based on the alleged frequency of their association. In two diseases, the Eaton–Lambert syndrome and the polyneuropathy of myeloma patients, this association is very striking, suggesting that indeed the underlying neoplams may cause the neurological disorders in the same way.

Eaton–Lambert syndrome satisfies several criteria of a truly paraneoplastic disease. In patients with this syndrome, malignant tumours are frequent. For instance, of 40 patients reported from the Mayo Clinic 28 (70%) has malignant tumours and 20 out of 28 were small cell lung carcinomas. Another interesting feature of this syndrome is its response to the treatment of the mulignant tumour. However, details concerning such remissions are scarce [6].

Finally, an acetone extract of cancer tissue from a patient with Eaton–Lambert syndrome has been shown to produce *in vitro* a defect in neuromuscular transmission in a frog nerve–muscle preparation by reducing the release of acetylcholine from motor nerve endings [7]. This observation suggests the production by the tumor of a factor able to modify the neuromuscular transmission, but the substance has not been yet isolated and characterized.

Peripheral neuropathies of myeloma patients, which occur without amyloidosis deposit, also suggest a remote action of the neoplastic tissue on the nervous system. In the osteoblastic variety of myelomas such polyneuropathies are seen in one third of the cases, and according to Davis and Drachmann [8] they frequently improve after radiotherapy of the neoplasm. In the same cases reported by Waldenström and Japanese authors, polyneuropathy is associated with other disorders such as skin pigmentation and thickening, peripheral oedema, excessive perspiration, gynaecomastia in males, frequent diabetes mellitus and hypertrichosis [3].

2. VIRAL INFECTIONS

Immunodepression of cancer patients due in part to the neoplastic disease itself, and partially to various treatment modalities including surgery, radiotherapy, chemotherapy and administration of corticosteroids, increases the incidence of infections, especially in patients with lymphomas and leukemias. The infectious agents include viruses which have been implicated in the pathogenesis of several carcinomatous neuropathies.

Herpes zoster, which is the most frequent infection of nervous system seen in as much as 25% of patients with lymphoma, particularly Hodgkin's disease, has never been considered as a carcinomatous neuropathy. But progressive multifocal leukoencephalopathy (PML), caused by a papovavirus is still often classified among carcinomatous neuropathies despite the fact that the pathogenesis of *Herpes zoster* and PML is the same, i.e. increased sensitivity to viral infections.

Viral etiology is also suggested by the pathology in other forms of carcinomatous neuropathies especially in diffuse polyoencephaliomyelities, where inflammatory reaction characterized by lymphocytic infiltrates is often disproportionate as compared to the degenerative neuronal changes. However, viral etiology has not been demonstrated in this group of diseases.

3. IMMUNOLOGICAL FACTORS

Because autoimmune reactions are seen in patients with cancer and also because this mechanism has been advocated in the pathogenesis of neurological disease such as multiple sclerosis or the Guillain–Barré syndrome, the hypothesis has been raised that at least some carcinomatous neuropathies are due to antibodies produced against tumour antigens cross-reacting with the nervous structures.

The presence of serum antibodies reacting with human brain tissue was investigated by Wilkinson [9] in patients with various types of carcinomatous neuropathies by using the complement-fixation test, and by Wilkinson and Zeromski [10] using immunofluorescent techniques. Only patients with the sensory neuropathy initially described by Denny-Brown showed a high rate of positive results. It must be pointed out, however, that the presence of such antibodies may be the result rather than the cause of nervous structures damage.

4. NUTRITIONAL AND TOXIC FACTORS

Alimentary deficiencies, metabolic disorders and exogenous toxic factors have not been sufficiently investigated in patients with carcinomatous neuropathies.

Particularly in patients with peripheral neuropathies common causes such as diabetes, alcoholism or administration of neurotoxic drugs are not systematically reported.

In a prospective study of morphological changes of the neuromuscular biopsies taken from cancer patients, we have observed a very good correlation between loss of weight and alterations, suggesting the existence of subclinical peripheral neuropathy [11]. The role of

non-specific factors of the peripheral nerve is also stressed by the fact that signs of peripheral neuropathy were equally frequent in patients with chronic non-neoplastic lung diseases and in patients with lung carcinoma [12]. In both groups, however, neurological abnormalities were significantly more frequent than in the controls.

In conclusion, the so-called carcinomatous neuropathies account for a small percentage of neurological disorders seen in cancer patients. Their pathogenesis is complex. Truly paraneoplastic mechanisms are involved in metabolic encephalopathies secondary to abnormal secression of hormones in very rare cases of encephalopathy due to serum hyperviscosity and in carcinoid-syndrome myopathy. In other forms of carcinomatous neuropathies such as the Eaton–Lambert syndrome and the polyneuropathy seen in osteosclerotic myeloma patients a remote effect of cancer on the nervous system is suggested by the incidence with which the disorders are associated with malignancies, but has not been demonstrated. They are, of course, examples of remote effect of cancer on nervous tissue such as the production of the nerve growing factor by a human sarcoma causing the formation of a tumour of nervous origin [13], but none of the described cancerous neuropathies can be explained by this mechanism.

Viral etiology has been demonstrated in PML and is possible in diffuse polioencephalomyelitis.

Autoimmune reaction against nervous constituents have been reported only in the sensory neuropathy. However, the role of these reactions in the pathogen of this syndrome has not been elucidated.

The pathogenesis of other forms of carcinomatous neuropathies remains obscure. Therefore this diagnosis should not be made unless all other causes, especially metastases and neurotoxic effects of anticancerous treatments, have been carefully ruled out.

REFERENCES

1. BRAIN WR, ADAMS RD. (1965): Epilogue. A guide to the classification and investigation of neuromuscular disorders with cancer In: BRAIN L, NORRIS FH, eds. *The Remote Effects of Cancer on the Nervous System.* New York: Grune and Stratton, 1965: 216–221.
2. HILDEBRAND J. *Lesions of the Nervous System in Cancer Patients.* New York: Raven Press, 1978: 142.
3. WALDENSTRÖM JG. (Ed.) Nervous system. In *Paraneoplasia. Biological Signals in the Diagnosis of Cancer.* New York: John Wiley, 28–40.
4. SWASH M, FOW KP, DAVIDSON AR. Carcinoid myopathy. *Arch Neurol* 1975; **12**: 572–574.
5. PATTEN BM, OLIVER KL, ENGEL WK. Serotonin induced muscle weakness. *Arch Neurol* 1974; **31**: 347–349.
6. NORRIS FH, IZZO AJ, GARVEY PH. Brief report. Tumor size and Lambert-Eaton syndrome. In BRAIN L, NORRIS FH. *The Remote Effect of Cancer on the Nervous System.* New York: Grune and Stratton, 1965: 81–820.
7. FUKUMARA N, TAKAMORI M, GUTMANN L, CHOU SM. Eaton-Lambert syndrome: ultrastructural study of the motor and plates. *Arch Neurol* 1972; **27**: 67–78.
8. DAVIS LE, DRACHMANN DB. Myeloma neuropathy. *Arch Neurol* 1972; **37**: 507–511.
9. WILKINSON PC. Serological findings in carcinomatous neuromyopathy. *Lancet* 1964; **i**: 1301–1303.
10. WILKINSON PC, ZEROMSKI J. Immunofluorescent detection of antibodies against neurones in sensory carcinomatous neuropathy. *Brain* 1965; **88**: 529–538.
11. HILDEBRAND J, COERS C. The neuromuscular function in patients with malignant tumors. *Brain* 1967; **90**: 67–82.
12. WILNER EC, BRODY JA. An evaluation of the remote effects of cancer on the nervous system. *Neurology* 1968; **18**: 1120–1124.
13. WADDELL WR, BRADSHAW RA, GOLDSTEIN MN, KIRSCH WM. Production of human nerve-growth in a patient with liposarcoma *Lancet* 1972; **i**: 1365–1367.